Dose Reconstruction From Urinary Biomarkers Using Pharmacokinetic Models

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1 ABSTRACT

The use of biomarkers for human health risk assessment is attractive because they are an indicator of the dose that has actually entered the body by all routes. This is an important consideration given the need to include aggregate exposures from the diet and other pathways for pesticides. Quantitative relationships between biomarker and environmental concentrations are often unclear. The measured concentration in a urine sample depends on the route, magnitude and time-profile of the exposure, as well as the rates of absorption, metabolism and excretion. Pharmacokinetic (PK) models describe the dynamics of the chemical in the body. By inverting the appropriate mathematical expressions, the total absorbed dose can be calculated from the concentration of the parent compound or a metabolite in a spot urine sample. The goal of this paper is to review the assumptions used in interpreting urinary biomarkers and highlight the role of PK models in reconstructing dose from spot urine measurements. We will demonstrate the estimation method on the interpretation of urinary biomarker measurements for chlorpyrifos, a widely used organophosphate pesticide.

2 INTRODUCTION

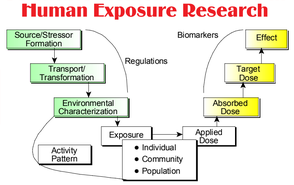
- Biomarkers are an important component of human exposure research
- They represent the total amount of a chemical that was absorbed by the body from all routes

Inhalation
Ingestion
Dermal

Biomarkers

- Proper estimation of total absorbed dose enables the evaluation of exposure to dose models
- The interpretation of biomarkers requires knowledge about the exposure scenario and the behavior of the chemical in the body

3 Scientific Elements Involved in Human Exposure Research



4 Biomarkers of Absorbed Dose

Evidence of exposure to a chemical that can be measured in tissues, fluids or excreted materials

- Inherently accounts for exposure from all routes
- Collection options are limited for human subjects (number of samples and media)

Urine samples

- Relatively simple to collect
- Contains concentrations of the parent compound or relevant metabolites

Role in Studies

- Survey studies: The timing of exposure is unknown relative to biomarker collection. The measurement is used in conjunction with questionnaires and activity data to estimate the exposure scenarios and associated absorbed dose.
- Monitored event study: Biomarker collection occurs both before and after the exposure event. The measurement is used to quantify the absorbed dose from the event.

5 Dose Estimation from a Urine Sample

Concentration (C_u) | Average Urinary Excretion Rate ($\overline{UER}$) | Absorbed Dose

1. Calculate the urinary excretion rate (UER, [μg/hr]), the rate at which the metabolite is excreted into the urine, from the urine metabolite concentration (C_u [μg/L]), urine volume (void volume, V_u [L]) and time since last void (t_c-t_v)

$$\overline{UER}\left[\frac{\mu g}{hr}\right] = \frac{C_u V_u}{t_c - t_v} = \left(\frac{\mu g\ metabolite}{L_{urine}}\right) \times \left(\frac{L_{urine}}{hr}\right)$$

   a) good when the total urine volume and time since last void are recorded; these may be difficult to obtain or unreliable for young children
   b) daily/hourly urine output can also be estimated from standard tables on urine production rates or creatinine concentration and excretion rates
   c) note that the UER accounts for variations in urinary water content

2. Assume a time profile for the absorbed dose based on reported activities
   a) Profiles may be constant (steady-state) or dynamic inputs (discrete events)
   b) Scenarios can be modeled based on a monitored event or questionnaire data

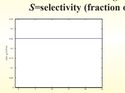
6 Dose Reconstruction

from the Calculated UER: Steady-State Assumption

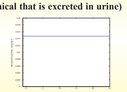
Assume a constant absorbed dose rate over time

$$ADr\left[\frac{\mu g}{kg \bullet day}\right] = \left(\frac{\overline{UER}}{bw}\right) \times \left(\frac{mw\ chemical}{mw\ metabolite}\right) \times \left(\frac{1}{S}\right)$$

where mw = molecular weight, and
S=selectivity (fraction of absorbed chemical that is excreted in urine)



Calculated UER of metabolite based on urine concentration 0.25 μg TCPY/hr



Estimated absorbed dose rate of chemical 0.015 μg chlorpyrifos/kg-hr

The steady-state model can also be used to approximate a repeating daily dose

7 Using a Pharmacokinetic (PK) model to Estimate Dose from an Exposure Event

We will focus on reconstructing events, as this is the more likely scenario based on the changing pattern of exposure (contact) activities for an individual.

1) Assume scenario for timing and routes (oral, dermal, inhalation) of exposure. The dynamics in the body are described by a PK model

$$\frac{d\mathbf{C}}{dt} = -\mathbf{K}\mathbf{C} + \mathbf{I}$$

where C are the body compartment concentrations, K are the PK model parameters (rate constants and compartment volumes) and I is the input vector. I and the initial conditions, $\mathbf{C}_o$, are functions of absorbed dose.

2) The calculated average UER is then compared to the solution of the PK model for the UER

$$\frac{V_u (C_u)_{measured}}{t_c - t_v} = \frac{1}{t_c - t_v}\int_{t_v}^{t_c} [C_u(\mathbf{t}, \mathbf{K}; dose)]_{model}\, dt$$

where t are the times since exposure and the previous void

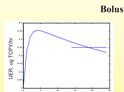
Note that for a linear PK model, the compartment concentrations are found from

$$\mathbf{C}(t) = \int_0^t e^{-\mathbf{K}(t-\tau)}\mathbf{I}(\tau)d\tau + e^{-\mathbf{K}t}\mathbf{C}_o$$

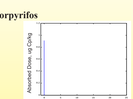
3) After integration of the expression for $(C_u)_{model}$, the dose is then an algebraic function of the measured urine concentration and the void volume

$$dose\left[\frac{\mu g}{kg\, bw}\right] = f[(C_u)_{measured}, V_u, \mathbf{t}, \mathbf{K}]$$

Bolus dose of chlorpyrifos



Calculated UER for metabolite, TCPY, 0.25 μg/hr

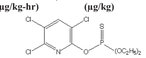


Absorbed oral dose, 0.91 μg Chlorpyrifos/kg bw

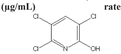
The timing and route must be assumed, since several exposure profiles could result in the same calculated UER

8 Chlorpyrifos Example: Pharmacokinetic Model (Nolan et al., 1984)

Chlorpyrifos: Intake (μg/kg-hr) | absorbed dose (μg/kg)



TCPY (metabolite): body conc TCPY (μg/mL) | urinary excretion rate, UER (μg/hr)



The compartment concentrations are described by

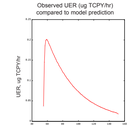
$$\frac{d}{dt}\begin{pmatrix} C_a \\ C_b \end{pmatrix} = \begin{pmatrix} -k_a & 0 \\ k_a & -k_e \end{pmatrix}\begin{pmatrix} C_a \\ C_b \end{pmatrix} + \begin{pmatrix} I_a \\ 0 \end{pmatrix}$$

where I_a is an absorbed dose rate (μg/kg-day),
C_a is the concentration in the intake compartment (skin, lungs, or gi tract), and
C_b is the concentration in the blood

Nolan, R.J.; Rick, D.L.; Freshour, N.L.; Saunders, J.H. Chlorpyrifos: Pharmacokinetics in Human Volunteers, *Toxicol. Appl. Pharm.* 1984, 73, 8-15.

9 Survey Data:

Reconstruction of an Oral Dose of Chlorpyrifos



Calculated UER from TCPY concentration measurements vs. model prediction. The model is the solid line, and the values based on measured concentrations are shown as +'s'. The data was taken from the Minnesota Children's Pesticide Exposure Study.

In this case, the timing of the dose is unknown. The time at which the dose occurred, the magnitude, and the background absorbed dose rate were fit to the inverted PK model equations by nonlinear optimization.

Possible Exposure Scenario

Background Dose Rate	Oral dose	Time of dose (hours before first sample taken)
0.2 μg/kg-day	3.3 μg/kg	8 hours

10 Biomarker Collection Options

for Absorbed Dose Estimation from a Monitored Application Event

Total Urine with Blood Collection Option #1	Total Urine Collection Option #2	Spot Urine Collection Option #3
Collect total urine for a designated number of days beginning with the exposure event, and blood measurements at the beginning and end of the study period	Collect total urine for 24 hours before, and sufficient days after the application event to ensure that all the absorbed chemical has been excreted	Collect spot urine (morning void) samples before the application event, 1 day after, and 3 days after the application event
2 Blood samples 1 composite urine sample	2 urine samples	3 urine samples

11 Model Uncertainty Comparison

for a Monitored Event: Chlorpyrifos Example

Ranges in Total Absorbed Oral Dose (μg/kg body weight) Estimations Reflecting the Model Uncertainty

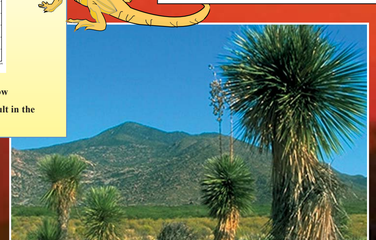
Total Absorbed Dose of Chlorpyrifos	Option #3: Spot Urine with sample volume and time recorded	Option #2: Ideal[1] Total Urine (5 day collection)	Option #1: Ideal[1] Total Urine with Blood Measurements
μg/kg body weight	2.0-10.2	2.6-8.9	2.6-8.0

[1]Ideal total urine schemes assume that no exposure to chlorpyrifos occurred after the studied event and that the blood/body partitioning is known exactly.

Note that the ideal total urine (Option #2) uncertainty range will approach the urine with blood (Option #3) uncertainty as the collection period is extended past 5 days.

CONCLUSION

In terms of the model uncertainty, it is possible to estimate dose with a similar range of uncertainty using a less burdensome collection scheme (spot urine samples as opposed to total collection).



12 SUMMARY

- Biomarker measurements can be used to estimate total absorbed dose from all routes
- Need to know the exposure scenario to interpret biomarker measurements
- For a monitored event, it is possible to estimate dose within similar uncertainty ranges using spot urine samples in place of total urine collection schemes

Further Research Needs

- Methods will be applicable for a wider range of chemicals as PK models are developed
- Reduction of model uncertainty will be possible as relevant data sets for the estimation of PK model parameters are obtained
- Reduced scenario uncertainty is dependent on improved analysis and classification of environmental concentration measurements, questionnaires, and activity data